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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,731	12/15/2003	Eberhard Weihe	029310.52995US	6798
23911 7590 08/11/2008 CROWELL & MORING LLP INTELLECTUAL PROPERTY GROUP P.O. BOX 14300 WASHINGTON, DC 20044-4300				
EXAMINER				
ULM, JOHN D				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/734,731

Applicant(s)

WEIHE ET AL.

Examiner

John D. Ulm

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1649

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 April 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5-10,13-15 and 33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-10,13-15 and 33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 December 2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1) Claims 1 to 3, 5 to 10, 13 to 15 and 33 are pending in the instant application. Claim 1 has been amended, and claims 4, 11 and 12 have been canceled as requested by Applicant in the correspondence filed 04 April of 2008.

2) Any objection or rejection of record that is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

4) A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04 April of 2008 has been entered.

Election/Restrictions

5) Claims 1 to 3, 5 to 10, 13 to 15 and 33, in so far as they relate to a method employing a polypeptide comprising one of the recited sequences other than SEQ ID NO:3 and 4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 13 April of 2005. It is unclear to the current examiner of record why claims 5, 6 and 13

have been indicated as withdrawn when they correspond to the originally elected invention. Those claims are being treated on the merits in the instant office action.

Drawings

6) The drawings filed on 15 December of 2003 do not comply with 37 C.F.R. § 1.84(U)(1), which states that partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a **capital letter**. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly.

Specification

7) The instant specification does not comply with 37 C.F.R. § 1.77, which requires that:

(a) The elements of the application, if applicable, should appear in the following order:

- (1) Utility Application Transmittal Form.
- (2) Fee Transmittal Form.
- (3) Title of the invention; or an introductory portion stating the name, citizenship, and residence of the applicant, and the title of the invention.
- (4) Cross-reference to related applications.
- (5) Statement regarding federally sponsored research or development.
- (6) Reference to a "Microfiche appendix." (See § 1.96 (c)). The total number of microfiche and total number of frames should be specified.
- (7) Background of the invention.
- (8) Brief summary of the invention.
- (9) Brief description of the several views of the drawing.
- (10) Detailed description of the invention.

- (11) Claim or claims.
- (12) Abstract of the Disclosure.
- (13) Drawings.
- (14) Executed oath or declaration.
- (15) Sequence Listing (See §§ 1.821 through 1.825).

(b) The elements set forth in paragraphs (a)(3) through (a)(5), (a)(7) through (a)(12) and (a)(15) of this section should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading. [43 FR 20464, May 11, 1978; 46 FR 2612, Jan. 12, 1981; paras. (h) and (i), 48 FR 2712, Jan. 20, 1983, effective Feb. 27, 1983; revised, 61 FR 42790, Aug. 19, 1996, effective Sept. 23, 1996].

Correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8) Claims 1 to 3, 5 to 10, 13 to 15 and 33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible specific and substantial asserted utility or a well established utility. The instant claims are drawn to a method of identifying a compound that binds to and effects the activity of a "BNPI" protein comprising the amino acid sequence presented in SEQ ID NO:4 of the instant application and then "determining whether the test substance is a pain-relevant substance".

The claimed method lacks utility in currently available form for several reasons. First, it is well established in the art of molecular biology that a compound that binds to and stimulates the activity of a particular protein is, by definition, an agonist of that

protein. It is also well established in the art that a compound that binds to and suppresses the activity of a protein is defined as an antagonist of that protein. It is further well established that an agonist and an antagonist of a particular protein have opposite physiological effects when administered to an organism with respect to those physiological processes that are mediated by that particular protein. The instant claims are inoperable because they do not distinguish between an agonistic and an antagonistic compound and because the instant specification and prior art of record fail to disclose whether it is the BNPI agonist or the BNPI antagonist that provides the alleged beneficial effect when administered to a subject.

The text in paragraph 0007 of the instant specification states that the starting point of the invention was the identification of pain-regulated genes which are modified in their expression under pain conditions and are therefore probably involved, via their regulation connections, in the development and processing of chronic pain". However, except for the pattern of expression of the recited proteins in neuronal cells, there is no evidence to support a conclusion that they are "involved" in the preceptor of pain. Further, there is absolutely no evidence that the activation or inhibition of a protein of the instant invention has a specific effect upon the perception of pain by an animal. It is a matter of law that an invention must have a specific and substantial utility "in currently available form", which precludes the need for further research, if that research is needed to establish a utility for the claimed invention (*Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct. 1966)). Before the claimed method has a practical utility, one must first establish a nexus between the activation of a protein of the instant invention and the

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perception of pain, or the inhibition thereof. The simple assertion that a protein of the instant invention "is probably involved" in the development and processing of chronic pain does not constitute an assertion of a specific and substantial utility. It actually constitutes nothing more than a starting point and a suggestion of how a specific utility for the claimed assay might be discovered upon further experimentation. The following is an excerpt from M.P.E.P. 2138.05:

"CLAIMED INVENTION IS NOT ACTUALLY REDUCED TO PRACTICE UNLESS THERE IS A KNOWN UTILITY

Utility for the invention must be known at the time of the reduction to practice. *Wiesner v. Weigert*, 212 USPQ 721, 726 (CCPA 1981) (except for plant and design inventions); *Azar v. Burns*, 188 USPQ 601, 604 (Bd. Pat. Inter. 1975) (a composition and a method cannot be actually reduced to practice unless the composition and the product produced by the method have a practical utility); *Ciric v. Flanigen*, 185 USPQ 103, 105 - 6 (CCPA 1975) ("when a count does not recite any particular utility, evidence establishing a substantial utility for any purpose is sufficient to prove a reduction to practice"; "the demonstrated similarity of ion exchange and adsorptive properties between the newly discovered zeolites and known crystalline zeolites ... have established utility for the zeolites of the count"); *Engelhardt v. Judd*, 151 USPQ 732, 735 (CCPA 1966) (When considering an actual reduction to practice as a bar to patentability for claims to compounds, it is sufficient to successfully demonstrate utility of the compounds in animals for somewhat different pharmaceutical purposes than those asserted in the specification for humans.); *Rey - Bellet v. Engelhardt*, 181 USPQ 453, 455 (CCPA 1974) (Two categories of tests on laboratory animals have been considered adequate to show utility and reduction to practice: first, tests carried out to prove utility in humans where there is a satisfactory correlation between humans and animals, and second, tests carried out to prove utility for treating animals.).

A PROBABLE UTILITY MAY NOT BE SUFFICIENT TO ESTABLISH UTILITY

A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." *Bindra v. Kelly*, 206 USPQ 570,

575 (Bd. Pat. Inter. 1979) (Reduction to practice was not established for an intermediate useful in the preparation of a second intermediate with a known utility in the preparation of a pharmaceutical. The record established there was a high degree of probability of a successful preparation because one skilled in the art may have been motivated, in the sense of 35 U.S.C. 103, to prepare the second intermediate from the first intermediate. However, a strong probability of utility is not sufficient to establish practical utility.); Wu v. Jucker, 167 USPQ 467, 472 (Bd. Pat. Inter. 1968) (screening test where there was an indication of possible utility is insufficient to establish practical utility). But see Nelson v. Bowler, 206 USPQ 881, 885 (CCPA 1980) (Relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses. Reasonable correlation between the two is sufficient for an actual reduction to practice.)."

Because the instant specification leaves it to the artisan to engage in the additional experimentation needed to determine if it is the BNPI agonist or the BNPI antagonist that provides the required beneficial effect in the treatment of pain, the claimed method lacks a specific and substantial utility in currently available form.

Second, there is absolutely no evidence or sound scientific reasoning of record that supports a conclusion that a compound that binds to and effects the activity of a "BNPI" protein comprising the amino acid sequence presented in SEQ ID NO:4 of the instant application will have any specific and predictable effect whatever on the perception of pain. It is noted that, in the related patent publication US 2004/0229217, which is based upon an application filed subsequent to the filing of the instant application, Applicant discloses essentially the same proteins and experimental data, presents claims to a binding assay, and alleges that the proteins described therein are involved in the mediation of "visual disturbances, retinitis pigmentosa, optical degeneration, hearing disorders, tinnitus, Meniere's disease, hearing loss, schizophrenia, manias, depression, stroke, cerebral trauma, paraplegia, amyotrophic

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lateral sclerosis, neuralgia, weight regulation, obesity, anorexia nervosa, epilepsy, hemiballism, Huntington's chorea, stress, Parkinson's disease, TIA (transient ischaemic attacks), emesis, dizziness, cataracts, arthritis, hyperactivity, developmental disorders, rabies, viral infections, bacterial infections, influenza, malaria, Creutzfeldt-Jacob disease, inflammatory bowel disease, Crohn's disease cardiovascular and cardiorespiratory functional disorders, hypertonia, disorder~ of baroaffference or chemoaffference, toxoplasmosis, asthma, autoimmunity in the, central and peripheral nervous system, diabetic neuropathy, autoimmunediabetes, alcoholic neuropathy, HIV-neuroAIDS; disorders of the autonomous nervous system, disorders of the nervous system of the digestive tract, oversensitivity, neurodegeneration, Alzheimer's disease, ischaemia; encephalitis, prion disease, Rasmussen's encephalitis, HIV encephalitis, demyelination, retinal degeneration, glaucoma, nystagmus, detachment of the retina, diseases the cerebellum, cerebellar ataxia, diseases of the basal ganglia, diseases of the pallidum, diseases of the organ of hearing or balance, diseases of the auditory canal or vestibular canal, memory disorders, learning disorders, cognitive disorders, stiff man syndrome, restless leg syndrome, anxiety, phobias, sleep disorders; drug dependency, addiction or withdrawal; hepatoencephalopathy with alcohol intoxication, hepatoencephalopathy without alcohol intoxication, diseases of neurotoxicological origin, diseases of the spinal motor neuron, muscular atrophies, muscular dystrophies, diseases of the posterior funiculus, alcoholic neuropathies, neuroinflammation, disturbances in the state of mind in the case of infections or fever, stress, taste disorders, food allergies, Chinese restaurant syndrome, aggression, paranoia, brain

concussion, neuroendocrine disorders, Tourette's syndrome, cerebrovascular spasms, neuronal apoptosis, neurodegeneration, neuronal necrosis, astrocytosis, burn-out syndrome, sudden infant death, heart attack, insomnia, retrograde amnesia, multiple sclerosis, jet lag, disorders of sexual function, or having activity for promoting microglia activation, learning, cognition or memory, for neuroprotection, for the liquor diagnosis of neurostatic diseases or for adjuvant therapy by electrostimulation of the nucleus subthalamicus in Parkinson's disease". Clearly, the expression patterns of the recited proteins were insufficient to convince even Applicant that they are specifically involved in the perception of pain

The claims assay lacks specific and substantial utility in currently available form because there is no evidence that a protein of the instant invention has increased or decreased **activity** in any particular disease or disorder that results in chronic pain or that the stimulation or inhibition of that activity will provide therapeutically beneficial effect. There mere fact that the level of expression of a protein changes in pathologies producing chronic pain does not support a conclusion that the protein has a causal role in that process or that one can reliably predict what effect a compound that binds to that protein is going to have on the perception of that pain. Applicant is advised that a statement of a specific utility is treated as true if it would be believed to be true by one of ordinary skill in the art given the evidence of record. Because there is absolutely no evidence provided by the instant specification or the prior art of record that one can reasonably predict that a compound that binds to a transporter protein of the instant invention is going to have a specific effect upon the perception of chronic pain, the

utilities asserted in paragraph 0016 of the instant specification are not credible to one of ordinary skill in the art of receptor biology in view of the evidence of record, or more precisely, the lack thereof. "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant 's assertions", (M.P.E.P. 2106.02 II(b)(1)(ii)).

Claim Rejections - 35 USC § 112

9) Claims 1 to 3, 5 to 10, 13 to 15 and 33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Further, these claims encompass a binding assay that can employ a "BNPI" protein having other than its entire native amino acid sequence. With respect to the limitation "the protein BNPI", the metes and bounds of that limitation are undeterminable. However, the instant specification does not provide the guidance needed to practice the claimed process with a "BNPI" polypeptide comprising anything less than the entire amino acid sequence presented in SEQ ID NO:2, 4, 6 or 8. The only manner described in the instant specification of using the claimed method is in the identification of compounds that have potential medicinal use because of their ability to agonize or antagonize one of the four mammalian transporter proteins described therein. The claimed invention is only useful in so far as the transporter protein

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employed in the claimed assay responds in a manner that is predictive of an authentic physiological response. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

One of ordinary skill in the art of receptor biology would not reasonably believe that the majority of physical peptide embodiments having at least to amino acids in common with SEQ ID NO:2, 4, 6 or 8 are going to be functional, much less be capable of producing an authentic response. Because the instant specification does not identify those amino acid residues in SEQ ID NO:2, 4, 6 or 8 which are critical to the structural and functional integrity of a transporter receptor protein comprising that sequence, identify a structurally analogous protein for which this information is known and could be applied to the instant protein by extrapolation, or even provide a single working example of an intentionally modified transporter protein of the instant invention, an artisan can not change even a single residue within the amino acid sequence of SEQ ID NO:2, 4, 6

or 8 and predict the effects of that change on the performance of that protein "by resort to known scientific law". Unless one can predict, with reasonable confidence, that an intentionally modified transporter protein is going to produce a response that is predictive of a native mammalian transporter protein, the information obtained from a process that uses that modified protein is of no practical value even if that protein had an established relationship with a particular disease or disorder.

10) Claims 1 to 3, 5 to 10, 13 to 15 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10.1) Claims 1 to 3, 5 to 10, 13 to 15 and 33 are vague and indefinite in so far as they employ the term "BNPI" as a limitation. Because the instant specification does not define this term nor does it identify that property or combination of properties which is unique to and, therefore, definitive of "the protein BNPI" an artisan can not determine if a compound which meets all of the other limitations of a claim would then be included or excluded from the claimed subject matter by the presence of this limitation. Whereas prior art references such as the Ni et al. patent (5,618,677) employ the term "hBNPI protein" to described a specific Na^+ -dependent inorganic phosphate cotransporter that occurs naturally in the human brain, Applicant can not rely upon such references to define the metes and bounds of the limitations contained in the instant claims.

10.2) Claims 1 to 3, 5 to 10, 13 to 15 and 33 are vague and indefinite because there is no antecedent basis for "the protein BNPI". The text in paragraph 0030 of the

instant specification indicates that there are at least four distinct proteins that are encompassed by the term "BNPI" as this term is employed therein.

10.3) The phrase "cultivated under conditions which allow expression" in claim 7 renders this claim vague and indefinite because the identity of the element or elements being expressed is not specified. Claim 98 is vague and indefinite in so far as it depends from claim 7 for this element.

Relevant Prior Art

11) The Ni et al. patent (5,618,677) is being cited because it described a "Human brain sodium dependent inorganic phosphate cotransporter" whose amino acid sequence is essentially identical to SEQ ID NO:4 of the instant application. The text from line 55 in column 28 to line 15 in column 29 therein, described a process of identifying "agents which act as antagonists or agonists of the hBNPI protein" by employing a "method comprising contacting a functional compound of the hBNPI protein with said substance, monitoring binding activity by physically detectable means, and identifying those substances which effect a chosen response". The method of Ni et al. is not materially different from those of the instant claims except for the recitation of the limitation "determining whether the test substance is a pain-relevant substance" in the instant claims. Nothing in the instant application or the Ni et al. patent supports Applicant's assertion that a compound that binds to the sodium dependent inorganic phosphate cotransporter of Ni et al. would be expected to have a specific and predictable effect upon the perception of pain by an individual.

Response to Arguments

12) Applicant's arguments filed 04 April of 2008 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (571) 272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John D. Ulm/

Primary Examiner, Art Unit 1649